**IN THE UNITED STATES DISTRICT COURT FOR THE MIDDLE DISTRICT OF TENNESSEE NASHVILLE DIVISION**

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| **RUTH SMITH, Individually and as Widow for the Use and Benefit of Herself and the Next Kin of Richard Smith, Deceased,** | ) | |
| **Plaintiff,** | ) | **Civil No. 3:05-0444** |
| | ) | **Judge Aleta A. Trauger** |
| **v.** | ) | **(Dist. Of MA No. 1:05-cv-11515PBS)** |
| **PFIZER INC., *et al.*,** | ) | |
| **Defendants.** | ) | |

## TESTIMONY OF HENRY G. GRABOWSKI

My name is Henry Grabowski. I live in Chapel Hill, North Carolina, and am a Professor of Economics at Duke University. My academic and research specialties are the pharmaceutical industry, economics of innovation, government regulation of business, and industrial organization. I have studied the economics of pharmaceuticals over most of my career. In fact, the first PhD dissertation I supervised back in 1974 addressed the subject of the depreciation (or decay) of pharmaceutical advertising.

I received my B.S. degree from Lehigh University in 1962. In 1967, I obtained a Ph.D. in Economics from Princeton University. I have been Director of the Program in Pharmaceuticals and Health Economics at Duke University since 1983. I have also held visiting scholar appointments at the International Institute of Management in Berlin, Germany, the Health Care Financing Administration in Washington, D.C., the Office of Health Economics in London, and the Centre for Medicines Research in London.

Under a series of grants from the National Science Foundation and other organizations, I have investigated a number of economic and policy issues involving the pharmaceutical industry.

I teach an advanced economics seminar at Duke on business innovation and lecture in a course called "Economics and Management of the Pharmaceutical Industry," a course that I created. Until last year I was associate editor of the Journal of Research in Pharmaceutical Economics, a position I held for about 10 years.

Over the years I have done a significant amount of work for the U.S. government on a variety of economic issues. I have testified several times before Congressional committees and U.S. regulatory bodies on pharmaceutical industry issues. I have been an advisor and consultant to the National Academy of Sciences, the Institute of Medicine, the Federal Trade Commission, the General Accounting Office, and the Office of Technology Assessment. I have published a number of books and over 50 peer-reviewed articles in the field of economics of pharmaceuticals. Finally, I have also served as an expert witness in several prior legal cases involving the pharmaceutical industry. A copy of my current c.v. is marked as **EXHIBIT 7447**.

I have been asked by counsel for the Pfizer defendants to address whether Dr. Charles King, Plaintiff's economic expert, has provided a valid economic or statistical basis for concluding that any specific Neurontin prescriptions were caused by any specific alleged misrepresentations on the part of the defendants. I have also been asked to address certain assertions made by Dr. King in his report concerning Pfizer's marketing and promotional efforts with respect to Neurontin and the off-label prescribing of the drug by physicians.

I have prepared a slide summarizing my opinions in this matter. **[SHOW DEMONSTRATIVE: SUMMARY OF OPINIONS]**

As an initial matter, it is important to keep in mind that Dr. King is not offering the opinion that Mr. Smith's particular Neurontin prescription was caused by allegedly improper off-label promotion. Dr. King has done no analysis specific to Mr. Smith or anyone else who has

taken Neurontin. Dr. King was not familiar with the facts of Mr. Smith's case at the time he was deposed in this litigation. In short, Dr. King has not attempted to provide valid economic evidence linking the specific prescription of Neurontin given to Mr. Smith to any alleged misrepresentation by the defendants.

As I will discuss in some detail, Dr. King has not offered an economic basis for his conclusions in this case that increases in Neurontin prescriptions for various off-label indications are attributable to allegedly improper promotion. Dr. King broadly asserts that certain charts provided to him of Neurontin use for off-label indications over time illustrate the impact of allegedly fraudulent promotion on off-label Neurontin use. Dr. King points to, among other things, the use of sales representatives, medical liaisons, CME programs and conferences, consultants meetings, advisory boards, and teleconferences for physicians as examples of alleged improper promotion and significant contributing factors to the off-label sales of Neurontin. He also highlights the publication of allegedly misleading articles and the alleged omission of references to studies with negative results. However, none of these activities, alone or in combination, proves that an increase in off-label use of Neurontin was caused by improper promotion.

For example, Dr. King relies on a chart that displays the number of sales calls to a group of psychiatrists alongside the number of prescriptions written by these psychiatrists over time. No attempt is made to account for other factors that likely influenced these prescriptions. Instead, Dr. King simply assumes that (a) the sales calls were all fraudulent; and (b) the sales calls caused substantially all of the prescriptions written by this group of psychiatrists. The basis for this assumption is simply that both sales calls and prescriptions increased over time – i.e., there is an asserted correlation in the trends depicted on the chart. Dr. King's assumption has no economic

or statistical validity.

First, Dr. King has done no analysis of the extent of correlation shown in Plaintiff's counsel's chart and he overlooks important differences in the patterns shown of promotion and prescriptions. Second, and more fundamentally, even if a correlation existed, it would not prove causation. Simple correlation between two variables does not provide a measure of how much one variable affects the other if additional influencing factors are omitted from the analysis. A correlation is not causation. For example, as cars have gotten safer over time with the addition of airbags and other new technologies, automobile fatalities have actually increased over time. No one would conclude that safer cars cause more automobile deaths. Obviously confounding variables, such as in increase in drivers, must be taken into consideration in understanding the relationship between these two factors.

Second, Dr. King's causal assertion is contrary to standard economic practice that attempts to measure the causal impact of one factor (in this case the allegedly improper promotion) on an outcome variable (in this case Neurontin's off-label usage) by isolating the effect of that one factor from the effect of other factors that influence the outcome variable. In order to prove that the allegedly improper promotion caused the overwhelming majority of off-label Neurontin use, Dr. King must establish that other factors had no significant effect on Neurontin's off-label use. Apart from the allegedly improper promotion, Dr. King has not addressed any of the various factors that may have affected off-label use of Neurontin.

As Dr. King himself has acknowledged, many factors affect off-label prescribing of prescription medications. **[SHOW DEMONSTRATIVE: OFF-LABEL PRESCRIBING]** A review of the literature and expert reports in these cases reveals uniform consensus that there are numerous factors unrelated to allegedly improper promotion that can affect off-label prescribing.

This conclusion is unsurprising and is consistent with my years of experience as an economist specializing in healthcare issues. Moreover, the literature and expert reports in this case reveal that Neurontin in particular has characteristics making it especially suitable for off-label prescribing. Any economist seeking to explain the causes of Neurontin off-label prescribing would have to develop an understanding of all these general and Neurontin-specific factors likely affecting off-label prescribing of Neurontin and control for them in his or her analysis. Dr. King, however, has not addressed or even acknowledged any factor other than alleged improper promotion, much less attempted to control for them.

As an initial matter, off-label prescribing (i.e., the use of an FDA-approved drug for an indication other than an indication approved by the FDA) is a common phenomenon and accepted clinical practice. Physicians are the main decision makers in the prescribing of drugs such as Neurontin and aim to find the best available treatment option for their patients. In fulfilling those obligations, physicians will often conclude that an off-label treatment is best. Otherwise stated, lack of FDA approval for a particular indication does not mean that a drug should not be prescribed.

It cannot be disputed that physicians choose to write off-label prescriptions for a variety of reasons. One reason is that the pace of medical and scientific discoveries is much faster than the FDA approval process. Not only is medical research continuously performed and reported, but physicians also test medications to see the results and discuss those results with colleagues. Indeed, the off-label use of a drug for a particular indication is frequently endorsed in medical reference guides long before the drug receives FDA approval.

A second reason that off-label prescribing is common is that, for many indications, the available FDA-approved medications do not provide adequate treatment for a large number of

patients. In such situations, physicians will innovate and try new drugs when theory suggests there may be a benefit to a patient. This is especially true when on-label treatment options are limited, or have many contraindications. A contraindication is a specific situation in which a particular drug or treatment should not be used because it may be harmful to the patient. Off-label prescribing is particularly common among anti-epileptic drugs ("AEDs"), including Neurontin. Therefore, it cannot simply be presumed that high off-label usage levels or sharp increases in off-label use are the result of improper promotion. Particularly in the case of AEDs, such patterns are common and may be attributable to numerous factors.

**[SHOW DEMONSTRATIVE: FACTORS INFLUENCING OFF-LABEL PRESCRIBING]**

Not unlike other decision-making situations, prescription decisions are based on a wide range of factors that are specific to each prescribing physician and patient. Such factors include, among other things, knowledge of the efficacy and side-effect profile of a drug, availability of alternative drugs to treat the patient's condition, knowledge of the benefits of using a drug in closely related indications, and knowledge of the use of similar drugs to treat the relevant indication. A wide range of factors affect drug prescriptions. Physicians accumulate knowledge about a drug from a number of different sources including: physicians' experiences prescribing the drug and observing its efficacy and side effects, published research, medical reference guides, discussions with colleagues, lectures and conferences, and theories advanced by scientists and scientific bodies.

Developments over time will also affect this pool of knowledge from which physicians draw in making their prescribing decisions. Among many other things: new articles may come out in academic publications, reference guides, and other sources, as clinical research is

conducted; new FDA approvals may occur, suggesting additional potential uses for a particular medication or related medications; approvals in foreign countries may affect prescribing decisions; and the medical community's growing experience with a medication, or class of medications, may lead to new discussions, new prescription ideas, and new standards of care.

The role of experience in determining prescribing decisions is significant because prescription medications are what we economists call "experience goods". Simply put, an experience good is a product you need to try to see how it works. Neurontin and other drugs are experience goods. Physicians learn about the efficacy, side-effect profile, and contraindications of drugs over time. Medical experts and doctors in this case uniformly confirm this point. In fact, Dr. King himself concedes that prescription medications are experience goods. If patients and physicians did not experience positive results with Neurontin, patients would not have continued to use it and physicians would not have continued to prescribe it. Dr. Mackey, one of Mr. Smith's prescribing physicians, has testified to the importance of past experience with Neurontin as an influence on his current decisions to prescribe Neurontin for off-label uses.

It is likely that numerous factors would have led to significant off-label prescribing of Neurontin wholly apart from any alleged improper promotion, including: the prevalence of off-label prescribing in general; the characteristics of Neurontin that make it an obvious candidate for off-label prescribing; physicians' positive experiences with Neurontin and other AEDs in treating the relevant conditions; and the numerous developments over time pertaining to Neurontin that likely underscored Neurontin's utility in treating a variety of off-label conditions and contributed to such uses.

As confirmed by several of the medical experts who have submitted reports in this litigation, Neurontin is a good candidate for off-label use because of its lack of drug-drug

interactions, contraindications, and demonstrated efficacy for off-label conditions with few alternative treatment options. Dr. Peter Donofrio, a neurologist who treats neuropathic pain, explained in his expert report that neuropathic pain is extremely difficult to treat and many patients do not respond adequately to the first or second medication prescribed. Drug interactions are common with these patients as they are often taking many other medications. Neurontin, however, has a limited potential for drug interactions. He describes Neurontin as "a safe and effective treatment for neuropathic pain and for years has been considered and continues to be considered one of the drugs of choice for treating neuropathic pain."

Numerous developments occurred prior to Mr. Smith's prescriptions of Neurontin that likely contributed to the increase in off-label prescribing of Neurontin and would have done so in the absence of any allegedly improper promotion. Dr. King's report fails to assess and quantify the effect of any of these developments or other factors on Neurontin's off-label usage.

For example, new information became available regarding the efficacy of Neurontin. Neurontin received FDA approval for the treatment of post-herpetic neuralgia, a form of neuropathic pain, in 2002. In Europe, Neurontin received broad approval for treatment of neuropathic pain in 2000, and by 2002 had been approved for treatment of neuropathic pain in over 60 markets. These and other developments likely would have contributed to significant levels of off-label prescribing in the absence of any alleged improper promotion.

Dr. King has acknowledged that there are numerous likely alternative causes of off-label Neurontin prescriptions, including a patient's experience with the drug and the physician's perception of how the patient is experiencing the drug. Other likely alternative causes of off-label Neurontin prescriptions besides off-label promotion that were acknowledged by Dr. King include: permissible on-label marketing, colleagues' experience, the Physicians' Desk Reference,

labeling, the medical literature, continuing medical educational events, a medical conference, a physician's own past experience using other drugs in the same therapeutic category, past experience with the drug, and standard reference works.

Finally, Dr. King's report suffers from numerous flaws and limitations. **[SHOW DEMONSTRATIVE: FLAWS IN DR. KING'S ANALYSIS]**

As an initial matter, as I already mentioned, Dr. King has offered no valid economic or statistical basis for concluding that any particular Neurontin prescriptions were caused by any particular alleged misrepresentation by defendants. He has done no case-specific analysis pertaining to Mr. Smith and he has no case-specific conclusions.

More generally, Dr. King conceded that he has not done any causation analysis specific to Neurontin. He has performed no analysis of the causes of the trends he observes in his data. In particular, Dr. King has done nothing to account for the numerous other causes of prescriptions besides promotion, including doctors' and patients' experiences, even though he conceded that drugs are experience goods. He also conceded that there would have been off-label prescriptions in the absence of any alleged improper conduct. Dr. King's only apparent attempt to conduct an analysis specific to Neurontin is a chart purporting to show some correlation between the prescriptions of certain psychiatrists and detailing. This "correlation" is questionable. Off-label prescribing by these psychiatrists was on the rise before any detailing started and continued long after detailing stopped. In any event, even if correlation existed, it would not prove causation, for the reasons I already discussed.

Dr. King relies on general assertions about the economic literature of pharmaceutical promotion to attempt to substantiate his claims about Neurontin. However, none of the literature he cites offers any Neurontin-specific analysis of the impacts of promotion, and it is not valid for

Dr. King to generalize from that literature to this case.

First, none of the literature relates to alleged fraudulent promotion. This is an important distinction because, as Dr. King concedes, prescription drugs are experience goods, meaning that patients and physicians can discern their quality and utility based on trying them. Any false or misleading messages about a prescription drug would be unlikely to have long-lived effect because they will be revealed as inaccurate as physicians and patients learn about the drug from their own experience. The fact that Neurontin sales have increased steadily over time, even in the face of allegations of improper marketing, suggest that positive experiences with Neurontin are a key factor driving sales.

Second, even if literature regarding the impact of truthful pharmaceutical promotion were relevant and could be applied to this case, it would not support Dr. King's conclusion that Neurontin promotion had a substantial impact on most prescribing of Neurontin. Therefore, no conclusions can be drawn without doing a valid analysis that is specific to the case at hand and that appropriately accounts for alternative causes of prescriptions other than promotion.

There is also no basis in the literature for Dr. King's assertion that effects of marketing and promotional stocks are long lived. The concept of "depreciation rates" is important when considering the effectiveness of any type of advertising or promotion. Depreciation is the diminishing impact over time of promotion. For example, a television or magazine ad will lose its effect unless it is shown repetitively over time. An analysis of recent pharmaceutical marketing studies indicates analyses of depreciation rates have been computed on monthly, quarterly, and annual data. These studies find depreciation rates for pharmaceutical marketing and promotional stocks that are generally in the range of 30%-60% when considered on an annual basis. Furthermore, Dr. King's own analysis of the anti-ulcer drug market in 2002 finds a

monthly depreciation rate of 7.4% for marketing or 60% per year. Other studies cited by Dr. King employ an annual depreciation rate of at least 30% or indicate that their results are not sensitive to the value of the depreciation rate over a wide range. Hence the consensus of the economic research on this issue does not support Dr. King's claim that the effects of off-label marketing would continue virtually unabated into the future, even after such promotion is terminated.

Dr. King also does not provide any valid basis for this conclusion that suppression of information about serious adverse affects enabled the growth in off-label sales of Neurontin. A product's side effect profile cannot be evaluated in isolation of other factors; rather it must be evaluated in terms of a product's overall clinical benefits and risks, and in comparison to what other therapeutic alternatives exist to treat a particular condition. To support his claims on the alleged suppression of side effects of Neurontin, Dr. King cites some academic studies where the sales of market share of a product were found to be inversely related to the number of its adverse effects. However these examples involve categories -- the H2 blocks for ulcers and SSRIs for depression -- where there are a number of relatively similar prescription medications or therapeutic options from the same chemical class. As discussed by Dr. Donofrio and others, the circumstances surrounding Neurontin off-label prescribing are very different from those surrounding the prescribing of SSRIs for depression or H2 blockers for ulcers. In particular, patients with neuropathic and chronic pain are generally faced with limited therapeutic options and are often found to be non-responsive to many of the available responsive therapies which do exist. Hence, it is inappropriate for Dr. King to generalize from experiences with these other drugs to the circumstances surrounding the off-label use of Neurontin at issue in this case.

Finally, Dr. King asserts that the pharmaceutical industry in general and Pfizer/Warner

Lambert in particular spend a much higher percentage of their revenues on marketing than on research and development. Dr. King's analysis of this issue exhibits a number of flaws. Dr. King's claims are based on comparisons of income statement data for selling, general and administration expenses (what we refer to as "SG&A") to Research and Development (or "R&D") expenditures. This is misleading on two accounts—first, the typical pharmaceutical company product mix is diversified across many business lines such as over-the-counter drug products, consumer products, and animal products, which involve less research intensive products than prescription drugs. Second, as its category name indicates, SG&A expenses encompass much more than promotional expenses for prescription pharmaceuticals. Professor Ernie Berndt, a well-respected researcher in my field, has examined the promotional intensity of the prescription drug industry using third party audit data. He finds the average promotional to sales ratio for the pharmaceutical industry in recent years has been relatively stable in the range of 14% to 15%. Furthermore, Professor Berndt finds that the marketing to sales ratio for other experience type goods (e.g. consumer non-durable goods such as packaged foods, vitamins, beverages, cosmetics, etc.) are typically much higher than for pharmaceuticals. By contrast, the R&D to sales ratios for prescription pharmaceuticals is generally among the highest of all industries, even compared to other high tech industries. A 2006 Congressional Budget Office analysis confirmed this fact. Furthermore, when non-pharmaceutical products are excluded from the computation, the R&D to sales ratios for the pharmaceutical industry have been in the neighborhood of 19% in recent years. This latter ratio is the appropriate comparator to Professor Berndt's marketing sales ratio of 14% to 15%. Hence, a careful analysis of the economic literature on this topic does not support Dr. King's allegation that marketing intensities exceed R&D intensities in prescription pharmaceuticals.

In summary, Dr. King has offered no opinions specific to Mr. Smith and this case, including whether Mr. Smith's Neurontin prescription was attributable to allegedly improper promotion of Neurontin. Nor has he provided an economic basis for the opinions he seeks to offer in this case regarding Neurontin and off-label prescribing patterns by doctors. His analysis is flawed for the reasons I have discussed and does not establish that Mr. Smith's doctors prescribed Neurontin to him because of any alleged misrepresentations by Defendants. My opinions are expressed to a reasonable degree of scientific certainty, and are based on my review of materials in this litigation as well as my education, training and experience as an economist.

Dated: April 27, 2010

Respectfully submitted,

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**CERTIFICATE OF SERVICE**

I hereby certify that on this the 27th day of April 2010, I electronically filed the foregoing document with the Clerk of the Court, United States District Court for the Middle District of Tennessee, using the CM/ECF system. True and correct copies of the foregoing documents are being served via the Court's CM/ECF system on the following:

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